

WE CLAIM:

1. A method for screening or diagnosis of ErbB2 related cancer in a subject, for determining the stage or severity of ErbB2 related cancer in a subject, for identifying a subject at risk of developing ErbB2 related cancer, or for monitoring the effect of therapy administered to a subject having ErbB2 related cancer, said method comprising:
 - (a) analysing a test sample of body fluid from the subject by two-dimensional electrophoresis to generate a two-dimensional array of features, said array comprising one or more of the ErbB2 Overexpression Features (EOFs) as defined in Table I; and
 - (b) comparing the abundance of the one or more EOFs in the test sample with the abundance of the one or more EOFs in a tissue or body fluid sample from one or more subjects free from ErbB2 related cancer, or with a previously determined reference range for that feature in subjects free from ErbB2 related cancer, or with the abundance at least one Expression Reference Feature (ERF) in the test sample.
2. The method according to claim 1 wherein the EOF is selected from one or more of the following EOFs: EOF-86, EOF-106, EOF-163, EOF-183, EOF-201, EOF-396, EOF-483, EOF-630, EOF-634, EOF-683 or EOF-693.
3. A method for screening or diagnosis of ErbB2 related cancer in a subject, for determining the stage or severity of ErbB2 related cancer in a subject, for identifying a subject at risk of developing ErbB2 related cancer, or for monitoring the effect of therapy administered to a subject having ErbB2 related cancer, said method comprising quantitatively detecting, in a test sample of body fluid from the subject, one or more of the ErbB2 Overexpression Protein Isoforms (EOPIs) as defined in Table III.
4. The method according to claim 3 wherein the EOPI is selected from one or more of the following EOPIs: EOPI-19, EOPI-22, EOPI-34, EOPI-59, EOPI-60, EOPI-62, EOPI-63, EOPI-92, EOPI-95, EOPI-115 or EOPI-125.
5. The method according to claim 1 where the body fluid is blood, serum, plasma or urine.
6. The method according to claim 3 where the abundance of the one or more EOPIs in the test sample is compared with the abundance of the one or more EOPIs in a sample from one or more subjects free from ErbB2 related cancer, or with a previously determined

reference range for that feature in subjects free from ErbB2 related cancer, or with the abundance at least one Expression Reference Feature (ERF) in the test sample.

7. The method according to claim 3, wherein the step of quantitatively detecting comprises testing at least one aliquot of the first sample, said step of testing comprising:
 - (a) contacting the aliquot with an antibody that is immunospecific for a EOPI;
 - (b) quantitatively measuring the binding of the antibody and the EOPI; and
 - (c) comparing the results of step (b) with a predetermined reference range.
8. The method according to claim 7, wherein the step of quantitatively detecting comprises testing a plurality of aliquots with a plurality of antibodies cognate for a plurality of preselected EOPIs.
9. A pharmaceutical composition comprising an ErbB2 Overexpression Protein Isoform (EOPI) as defined in claim 3, or a nucleic acid encoding an EOPI, and a pharmaceutically acceptable carrier.
10. The pharmaceutical composition according to claim 9, wherein the ErbB2 Overexpression Protein Isoform (EOPI) is in recombinant form.
11. An antibody capable of immunospecific binding to an ErbB2 Overexpression Protein Isoform (EOPI) as defined in claim 3.
12. The method according to claim 7, wherein the antibody is a monoclonal antibody.
13. The method according to claim 7, wherein the antibody is selected from a chimeric antibody, a bispecific antibody and a humanised antibody.
14. The method according to claim 7, wherein the antibody binds to the EOPI with greater affinity than to another isoform of the EOPI.
15. A kit comprising one or more antibodies as claimed in claim 11 and/or one or more EOPIs as defined in claim 3, other reagents and instructions for use.
16. The kit of claim 15 for use in the screening or diagnosis of ErbB2 related cancer in a subject, for determining the stage or severity of ErbB2 related cancer in a subject, for

identifying a subject at risk of developing ErbB2 related cancer, or for monitoring the effect of therapy administered to a subject having ErbB2 related cancer.

17. The kit according to claim 15 comprising a plurality of antibodies as claimed in claim 11 and/or a plurality of EOPIs as defined in claim 3.

18. A pharmaceutical composition comprising a therapeutically effective amount of an antibody, or a fragment or derivative of an antibody according to claim 11 and a pharmaceutically acceptable carrier.

19. A method of treating or preventing ErbB2 related cancer comprising administering to a subject in need of such treatment a therapeutically effective amount of an antibody as claimed in claim 11.

20. A method of treating or preventing ErbB2 related cancer comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more of the ErbB2 Overexpression Protein Isoforms (EOPIs) as defined in claim 3 and/or a nucleic acid encoding said EOPIs.

21. A method of treating or preventing ErbB2 related cancer comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of a nucleic acid that inhibits the function of one or more of the ErbB2 Overexpression Protein Isoforms (EOPIs) as defined in claim 3.

22. The method according to claim 21, wherein the nucleic acid is a EOPI antisense nucleic acid or ribozyme.

23. A method of screening for agents that interact with one or more ErbB2 Overexpression Protein Isoforms (EOPIs) as defined in claim 3, fragments of EOPIs (EOPI fragment), polypeptides related to EOPIs (EOPI-related polypeptide), or EOPI-fusion proteins said method comprising:

- (a) contacting an EOPI, an EOPI fragment, an EOPI-related polypeptide, or an EOPI-fusion protein with a candidate agent; and
- (b) determining whether or not the candidate agent interacts with the EOPI, the EOPI fragment, the EOPI-related polypeptide, or the EOPI-fusion protein.

24. The method according to claim 23, wherein the determination of interaction between

the candidate agent and the EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein comprises quantitatively detecting binding of the candidate agent and the EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein.

25. A method of screening for or identifying agents that modulate the expression or activity of one or more ErbB2 Overexpression Protein Isoforms (EOPIs) as defined in claim 3, fragments of EOPI (EOPI fragment), polypeptides related to EOPIs (EOPI-related polypeptide) or EOPI-fusion proteins comprising:

- (a) contacting a first population of cells expressing the EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein with a candidate agent;
- (b) contacting a second population of cells expressing said EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein with a control agent; and
- (c) comparing the level of said EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein or mRNA encoding said EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein in the first and second populations of cells, or comparing the level of induction of a downstream effector in the first and second populations of cells.

26. A method of screening for or identifying agents that modulate the expression or activity of one or more ErbB2 Overexpression Protein Isoforms (EOPIs) as defined in claim 3, fragments of EOPIs (EOPI fragment), polypeptides related to EOPIs (EOPI-related polypeptide) or EOPI-fusion proteins said method comprising:

- (a) administering a candidate agent to a first mammal or group of mammals;
- (b) administering a control agent to a second mammal or group of mammals; and
- (c) comparing the level of expression of the EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein, or mRNA encoding said EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein in the first and second groups, or comparing the level of induction of a downstream effector in the first and second groups.

27. The method as claimed in claim 26, wherein the mammals are animal models for ErbB2 related cancer.

28. The method according to claim 25, wherein administration of a candidate agent results in an increase in the level of said EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein, or mRNA encoding said EOPI, EOPI fragment, EOPI-related

polypeptide, or EOPI-fusion protein, or said downstream effector in the first population of cells or mammals compared to the second population of cells or mammals.

29. The method according to claim 25, wherein administration of a candidate agent results in a decrease in the level of said EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein, or mRNA encoding said EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein, or said downstream effector in the first population of cells or mammals compared to the second population of cells or mammals.

30. The method as claimed in claim 25, wherein the levels of said EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein, or mRNA encoding said EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein, or of said downstream effector in the first and second groups are further compared to the level of said EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein, or mRNA encoding said EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein in normal control mammals.

31. The method according to claim 30, wherein said mammals are human subjects with ErbB2 related cancer.

32. A method of screening for or identifying agents that modulate the activity of one or more of the ErbB2 Overexpression Proteins Isoforms (EOPIs) as defined in claim 3, fragments of EOPIs (EOPI-fragment), polypeptides related to EOPIs (EOPI-related polypeptide) or EOPI-fusion proteins said method comprising:

- (a) in a first aliquot, contacting a candidate agent with the EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein, and
- (b) determining and comparing the activity of the EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein in the first aliquot after addition of the candidate agent with the activity of the EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein in a control aliquot, or with a previously determined reference range.

33. The method according to claim 23, wherein the EOPI, EOPI fragment, EOPI-related polypeptide, or EOPI-fusion protein is a recombinant protein.

34. The method according to claim 23, wherein the EOPI, EOPI fragment, EOPI-related polypeptide or EOPI-fusion protein is immobilized on a solid phase.

35. A method for screening or diagnosis of ErbB2 related cancer in a subject or for monitoring the effect of an anti-ErbB2 related cancer drug or therapy administered to a subject, comprising:
- (a) contacting at least one oligonucleotide probe comprising 10 or more consecutive nucleotides complementary to a nucleotide sequence encoding an EOPI as defined in claim 3 with RNA obtained from a biological sample from the subject or with cDNA copied from the RNA wherein said contacting occurs under conditions that permit hybridization of the probe to the nucleotide sequence if present;
 - (b) detecting hybridization, if any, between the probe and the nucleotide sequence; and
 - (c) comparing the hybridization, if any, detected in step (b) with the hybridization detected in a control sample, or with a previously determined reference range.
36. The method as claimed in claim 35, wherein step (a) includes the step of hybridizing the nucleotide sequence to a DNA array, wherein one or more members of the array are the probes complementary to a plurality of nucleotide sequences encoding distinct EOPIs.
37. A method of modulating the activity of one or more of the ErbB2 Overexpression Protein Isoforms as defined in claim 3, comprising administering to a subject an agent identified by the method of claim 23.
38. A method of treating or preventing ErbB2 related cancer comprising administering to a subject in need of such treatment or prevention a therapeutically effective dose of an agent that modulates the activity of one or more of the ErbB2 Overexpression Protein Isoforms as defined in claim 3, whereby the symptoms of the ErbB2 related cancer are ameliorated.
39. A method for identifying targets for therapeutic modulation of ErbB2 related cancer wherein the activity of one or more of the ErbB2 Overexpression Protein Isoforms as defined in claim 3, is utilized as a measure to determine whether a candidate target is effective for modulation of ErbB2 related cancer.
40. A method according to claim 3 wherein the ErbB2 related cancer is selected from breast, ovary, stomach or lung cancer.
41. A method according to claim 40 wherein the ErbB2 related cancer is breast cancer.